

## REMARKS

Claims 1 to 23 are pending. Claims 1, 7 to 10 and 19 to 23 have been amended. Claim 1 has been amended to recite the ee range of the enantiomeric purity of the products based on the numbered examples in the application.

The Office Action stated: that Claims 1 to 6 and 23 are pending; and that Claims 1 to 23 are rejected.

The undersigned attorney thanks Examiner Sarah Pihonak and Supervisory Examiner Sreeni Padmanabhan for the courtesy of the interview on July 29, 2009. The undersigned attorney stated that the claimed process was a catalytic process and that catalytic was very unpredictable. He pointed out that applied U.S. Patent No. 6,878,665 (US '665) was also a catalytic process. The Examiner had cited '665 in combination with EP 1,176,135 (EP '135) as the basis of the obviousness rejection. He pointed out that US '665 directed away from the claimed invention, showing the unobviousness thereof, and that the data in US '665 shows that catalytic activity is very unpredictable. US '665 only shows fluoro compounds, whereas applicants claim chloro and bromo compounds. Applicants claim substituents that are one carbon containing one to three chloro or bromo atoms – applicants' numbered examples show that an enantiomeric purity of an ee of 93.2 to 98.1 percent. He said that this shown an unexpected advantage over US '665. In US '665, using the ruthenium-Fluoxphos complex (catalyst), Table 1 of US '665 shows ee's of 49 and 70 percent for  $-CF_3$  ee's of 63 and 75 percent for  $-C_2F_5$ , and an ee of 80 percent for  $-C_3F_7$ , and Table 2 shows an ee of 23 percent for  $-CF_3$ , and an ee of 44 percent for  $-C_2F_5$ . This data: directs one away from the unexpected advantage of applicants' claimed invention that gets ee's of at least 93.2 percent; and directs away from using the ruthenium-Fluoxphos complex (catalyst) with bromo or chloro on  $-CX_{1-3}H_{1-2}$  because of the very poor enantiomeric purity US '665 obtained even compared to its higher  $-C_2F_5$  and  $-C_3F_7$  substituents. The undersigned

attorney stated that the rejection was in error also because it had not combined the two rejection references in the manner that would be done by one ordinarily skilled in the art. He said that because EP '135 achieved very high ee's [with ethyl-4-chloroacetoacetate in Example (cited by the Examiner) the ee was 98.5 percent] using {Ru<sub>2</sub>Cl<sub>4</sub>((R)-SEGP<sub>2</sub>HOS)<sub>2</sub>](NEt<sub>3</sub>) catalyst, one ordinarily skilled in the art would use the SEGP<sub>2</sub>HOS catalyst of EP '135 in the reference combination rejection instead of the Fluoxphos catalyst of US '665 (which has the low ee's). All of the disclosure in the rejection references must be considered in making an obviousness rejection. The correct combination of the rejection references would contain a catalyst outside of the scope of applicants' claimed invention. The Supervisory Examiner said that independent Claim 1 did not contain any recitation/limitation that spelled out the high level of ee's obtained, and suggested that claims with a range of ee's based on the numbered examples would be considered. Independent Claim 1 now contains such an ee range.

The Office Action stated that the following is a quotation of 35 U.S.C. 103(a) which forms the basis for the obviousness rejection set forth in this Office Action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

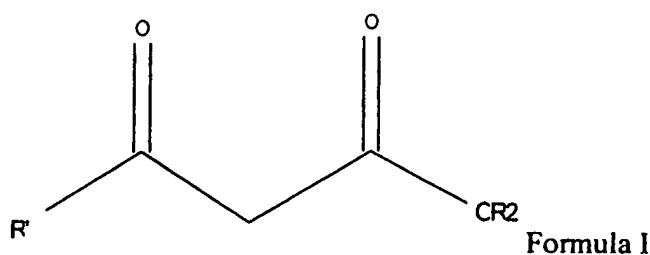
Claims 1 to 23 have been rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,878,665 (US '665) in view of EP 1176135 (EP '135), (provided by applicants on IDS of April 24, 2006). Applicants traverse this rejection.

The Office Action stated that regarding instant Claim 1:

U.S. Patent 6,878,665 (known hereafter as US '665) discloses a transition metal chiral catalyst that can be used for asymmetric hydrogenation. Claim 11 of US '665 (page 14, column 26) teaches that the transition metal may be ruthenium, while Claim 9 (page 14, column 25) teaches that the ligand attached to the ruthenium center is Fluoxphos. Claim 16 of US '665 broadly states that the asymmetric hydrogenation is performed on a substrate, and Table 1, pages 10 to 12 displays examples of substrates. Of particular interest is the hydrogenation of ethyl 4,4,4-trifluoro-3-oxobutylate, on page 12, Table 1.

The Office Action also stated that, regarding Claim 1, US '665 does not teach the following:

Instant Claim 1 recites that the ruthenium-Fluoxphos complex is to be used to prepare enantiomerically pure (S)- or (R)-halo-3-hydroxybutyrate from compounds of the formula shown below:



In which R' = CH<sub>2</sub>X, CHX<sub>2</sub>, or CX<sub>3</sub>, with X = Cl, and/or Br

and R<sub>2</sub> = C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, aryl, aralkyl, and each aryl or aralkyl may be substituted with one or more C<sub>1-4</sub> alkyl groups, and/or halogen atoms.

There are several things in and concerning original Claim 1 that US '665 does not teach or suggest. Furthermore, Claim 1 has been amended to recite the range of the very high ee's achieved by applicants' claimed process. Applicants believe that amended independent Claim 1 is not obvious over the combination of rejection references. Also, such claimed ee range of the claimed invention is an unexpected advantage showing patentable invention over the combination of rejection references (and over each

rejection reference individually).

The Office Action stated that US '665 does not recite in the claims specifically as to the type of substrates that the ruthenium-Fluoxphos catalyst is to hydrogenate. This fact directs away from applicants' claimed invention – the results of the US '665 tests also directs from the use of the Fluoxphos catalyst.

The Office Action, rather, on page 10, column 17, lines 17 to 19, states "The catalysts according to the invention for stereoselective hydrogenation are useful for carrying out reductions of the following type:", which is followed by examples in Table 1. Table 1's results direct away from applicants' claimed invention.

The Office Action stated that the substrates shown in Table 1 (pages 10 to 12) are not just 3-oxobutyrate; some the chain lengths are longer, or shorter. None such tested substrates are pertinent under Section 103(a) except to direct away from the claimed invention because such tested substrates do not have substituents containing Br or Cl.

The Office Action stated that, however, the R<sub>2</sub> group of the substrates shown in Table 1 are C<sub>1-4</sub> alkyl groups, as well as aryl. This is of no showing of obviousness.

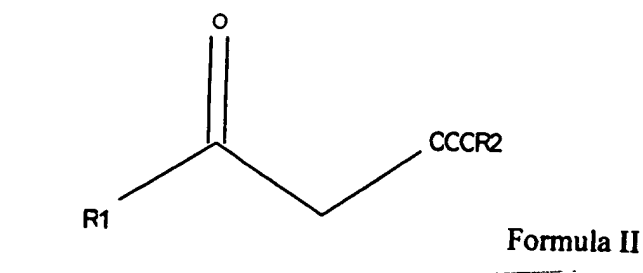
The Office Action stated that there are no examples in US '665 in which R<sub>2</sub> = C<sub>1-6</sub> cycloalkyl, aralkyl, or aryl/aralkyl groups optionally substituted with one or more C<sub>1-4</sub> alkyl groups and/or halogen atoms; and that there are also no examples of substrates in which R' = CH<sub>2</sub>X, CHX<sub>2</sub>, or CX<sub>3</sub>, with X = Cl and/or Br. This shows the lack of relevance of the reference in the quest for applicants' claimed invention

The Office Action also stated that, regarding Claim 1, EP 1176135 (known hereafter as EP '135) discloses the use of a ruthenium complex as a catalyst for asymmetric hydrogenation (the patent application of EP 1176135 was presented in the Information Disclosure Statement submitted by applicants). The Examiner has no basis in the record to generify the specific catalyst of EP '135.

The Office Action stated that the chiral ligand of the ruthenium catalyst is known as SEGPHOS, and is very structurally similar to the Fluoxphos ligand, with the exception that the bis(methylenedioxy)biphenyl moiety is replaced with bis(difluoromethylenedioxy)biphenyl. Such difference is major because catalytic activity is very unpredictable (as shown by the various involved data).

The Office Action stated that EP '135 discloses the use of the ruthenium-SEGPHOS complex for the asymmetric hydrogenation of ethyl 4-chloroacetoacetate to ethyl (S)-4-chloro-3-hydroxybutyrate (pages 9 and 10, Example 6). Such Example 6 shows that one ordinarily skilled in the art would use the SEGPHOS catalyst, instead of the Fluoxphos catalyst, in the rejection combination in the search for applicants' claimed invention. See the above report of the interview regarding this matter.

The Office Action stated that, additionally, EP '135 teaches that compounds of the formula shown below can undergo asymmetric hydrogenation with the ruthenium-SEGPHOS complex:



where R1 = C<sub>1-15</sub> alkyl group, in which the alkyl group may have one or more substituents selected hydroxyl, halogen, amino (which may be further substituted with one or more C<sub>1-4</sub> alkyl groups, ), benzyloxy, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkoxycarbonyl, and aryl groups, among others, and R2 may be among the following: C1-8 alkyl, or a benzyl

group, which may have one or more substituents (page 11, Claim 1).

EP '135 shows that the present rejection references incorrectly combined as regards what one ordinarily skilled in the art would do.

The Office Action stated that: however, EP '135 clearly teaches that many of the 4-halo-3-hydroxybutyrates of formula I can undergo asymmetric hydrogenation with the ruthenium –SEGPPOS catalyst, that Formula I R' substituents, which may be either CH<sub>2</sub>X, CHX<sub>2</sub>, or CX<sub>3</sub>, (in which X = Cl, and/or Br), are included in the possible R1 groups for formula II; and that Formula 1 R2 substituents, which may be either C<sub>1-6</sub> alkyl, aryl, or aralkyl (which may be substituted with one or more C<sub>1-4</sub> alkyl groups, and/or halogen atoms), would be included in the possible R2 substituents of formula II above. The high ee's of EP '135 shows that the SEGPPOS catalyst would be the one used by one ordinarily skilled in the art in the rejection combination.

The Office Action stated that EP '135 does not specifically teach that R2 of formula I may be C<sub>3-6</sub> cycloalkyl. Such reference, in the rejection combination, directs away from applicants' claimed invention.

Applicants have shown that amended (and original) independent Claim 1 is unobvious over the combination of two rejection references, therefore, all of the dependent claims are also unobvious over such rejection combination.

The Office Action stated that, regarding Claim 2, US '665 teaches all of the embodiments of paragraph 4 above, and additionally that the complex contains an alkene (ex. methylallyl, page 5, column 7, line 54), an arene (ex. benzene, page 5, column 8, line 8), a diene (ex. 1,5-cyclooctadiene, page 9, column 16, lines 60 to 65), and/or a polar solvent molecule (ex. pyridine, page 5, column 7, line 55). Applicants traverse this statement as being clearly incorrect as shown above. Obviousness has not been shown.

The Office Action stated: that, regarding instant Claim 3, US '665 teaches all of

the embodiments of paragraph 4, above, and additionally that the ruthenium-Fluoxphos complex has at least one ligand selected from 1,5-cyclooctadiene (page 9, column 16, lines 60 to 65), or p-cymene (page 5, column 8, line 8); and, regarding instant Claim 4, US '665 teaches all of the embodiments of paragraph 4, above; and that, furthermore, the hydrogenation is performed in solvents comprised of C<sub>1-4</sub> alcohols (page 5, column 8, lines 59 and 60), dimethylformamide (page 5, column 8, line 57), and further solvent additives, such as an acid (page 9, column 16, lines 60 to 65). The dependent claim is not obvious because the independent claim is unobvious.

The Office Action also stated that Claim 4 recites that the polar solvents to be used for the hydrogenation are selected from C<sub>1-4</sub> alcohols, dimethylsulfoxide, dimethylformamide, acetonitrile and mixtures thereof, and possibly further solvent additives. U.S. '665 states that the reaction solvents may be dimethylformamide, C<sub>1-4</sub> alcohols (page 5, column 8, lines 55 to 64), optional solvent additives (page 9, column 16, example 6a, lines 60 to 62), and other possible polar and non-polar solvents (page 5, column 8, lines 55 to 64); and that US '665 does not specifically state that the solvents may be dimethylsulfoxide or acetonitrile. The dependent claim is not obvious because the independent claim is unobvious.

The Office Action stated: that, regarding Claim 5, US '665 teaches all of the embodiments of paragraph 4 above, and that the counterion of the ruthenium complex may be of Cl<sup>-</sup>, Br<sup>-</sup>, I<sup>-</sup>, BF<sub>4</sub><sup>-</sup>, ClO<sub>4</sub><sup>-</sup>, PF<sub>6</sub><sup>-</sup>, (page 5, column 8, lines 8 to 10); that Claim 5 recites that the counterions for the ruthenium-Fluoxphos complex are selected from Cl<sup>-</sup>, Br<sup>-</sup>, I<sup>-</sup>, BF<sub>4</sub><sup>-</sup>, PF<sub>6</sub><sup>-</sup>, ClO<sub>4</sub><sup>-</sup>, OTf, AsF<sub>6</sub><sup>-</sup>, and SbF<sub>6</sub><sup>-</sup>; and that US '665 does teach that the counterions for the ruthenium-Fluoxphos complex are possibly Cl<sup>-</sup>, Br<sup>-</sup>, I<sup>-</sup>, BF<sub>4</sub><sup>-</sup>, PF<sub>6</sub><sup>-</sup>, ClO<sub>4</sub><sup>-</sup>, or NH<sub>2</sub>(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>, but does not specifically include OTf<sup>-</sup>, AsF<sub>6</sub><sup>-</sup>, and SbF<sub>6</sub><sup>-</sup> among the selection. Dependent Claim 5 is not obvious.

The Office Action stated: that, regarding Claim 6, US '665 teaches all of the

elements of paragraph 4 above, and additionally, that the ruthenium complex may be prepared by mixing a complex of formula  $[\text{Ru}_2\text{Cl}_4(\text{benzene})_2]$  with the Fluoxphos ligand in tetrahydrofuran (page 9, column 16, lines 10 to 17); and that the p-cymene ligand may be substituted for the benzene (page 5, column 8, line 8), and tetrahydrofuran fulfills the polar solvent requirement. Dependent Claim 6 is not obvious.

The Office Action stated: that, regarding Claim 7, US '665 teaches all of the elements of paragraph 4 above, with the addition that the asymmetric hydrogenation is performed with a hydrogen pressure range between 1 to 150 bar (page 6, column 9, line 16 and 17); and that this requirement meets the limitations of instant Claim 7, in which the hydrogen pressure is in the range of 1 to 60 bar during the hydrogenation. Dependent Claim 7 is not obvious.

The Office Action stated that, regarding Claim 8, US '665 teaches all of the elements of paragraph 5 above, and that at least one molecule of the ruthenium complex is 1,5-cyclooctadiene (page 9, column 16, lines 60 to 65), or p-cymene (page 5, column 8, line 8), Dependent Claim 8 is not obvious.

The Office Action stated: that, regarding Claim 9, US '665 teaches all of the elements of paragraph 5 above, and that the hydrogenation reaction can be performed with solvents such as  $\text{C}_{1-4}$  alcohols (page 5, column 8, lines 59 and 60), dimethylformamide (page 5, column 8, line 57), and additional solvent additives, such as an acid (page 9, column 16, lines 60 to 65); and that, with regard to Claim 9 – see statement for Claim 4 above. Dependent Claim 9 is not obvious.

The Office Action stated: that, regarding Claim 10, US '665 teaches all of the elements of paragraph 6 above, and additionally, the hydrogenation can be performed with solvents such as  $\text{C}_{1-4}$  alcohols (page 5, column 8, lines 59 and 60), dimethylformamide (page 5, column 8, line 57), and additional solvent additives, such as an acid (page 9, column 16, lines 60 to 65); and that, with regard to Claim 10 – see

statement for Claim 4 above. Dependent Claim 10 is not obvious.

The Office Action stated: that, regarding Claim 11, US '665 teaches all of the elements of paragraph 5 above, and also, that the counterion for the complex may be  $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{I}^-$ ,  $\text{BF}_4^-$ ,  $\text{PF}_6^-$ ,  $\text{ClO}_4^-$ , (page 5, column 8, lines 8 to 10); and that with regard to Claim 11 – see statement for Claim 5 above. Dependent Claim 11 is not obvious.

The Office Action stated: that regarding Claim 12 that U.S. '665 teaches all of the elements of paragraph 11 above, and also, that the counterion for the complex may be  $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{I}^-$ ,  $\text{BF}_4^-$ ,  $\text{ClO}_4^-$ ,  $\text{PF}_6^-$  (page 5, column 8, lines 8 to 10, and page 9, column 16, Example 6a); and that, with regard to Claim 12 – see statement for Claim 5 above. Dependent Claim 12 is not obvious.

The Office Action stated: that, regarding Claim 13, US '665 teaches all of the elements of paragraph 13 above, and also, that the counterion of the ruthenium complex may be  $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{I}^-$ ,  $\text{BF}_4^-$ ,  $\text{ClO}_4^-$ ,  $\text{PF}_6^-$  (page 5, column 8, lines 8 to 11, and lines 55 to 64; also page 9, column 16, lines 60 to 65); and that, with regard to Claim 13 – see statement for Claim 5 above. Dependent Claim 13 is not obvious.

The Office Action stated: that, regarding Claim 14, US '665 teaches all of the elements of paragraph 12 above, as well as the counterion may be  $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{I}^-$ ,  $\text{BF}_4^-$ ,  $\text{PF}_6^-$ , or  $\text{ClO}_4^-$ , (page 5, column 8, lines 8 to 11, and lines 55 to 64; also page 9, column 16, lines 60 to 65); and that, with regard to Claim 14 – see statement for Claim 5 above. Dependent Claim 14 is not obvious.

The Office Action stated: that, regarding Claim 15, US '665 teaches all of the elements of paragraph 5, and additionally, that the ruthenium-Fluoxphos complex can be prepared by combining  $[\text{Ru}_2\text{Cl}_4(\text{cym})_2]$  with the Fluoxphos ligand in a polar solvent (page 9, column 16, Example 2); and that while this example particularly discloses using  $[\text{Ru}_2\text{Cl}_4(\text{benzene})_2]$  p-cymene may substitute for benzene (page 5, column 8, line 8). Dependent Claim 15 is not obvious,

The Office Action stated: that, regarding Claim 16, US '665 teaches all of the elements of paragraph 11, and additionally, that a ruthenium-Fluoxphos complex can be prepared by mixing a compound of formula  $[\text{Ru}_2\text{Cl}_4(\text{cym})_2]$  with the Fluoxphos ligand in a polar solvent (page 9, column 16, Example 2); and that while this example discloses the formation of the complex using  $[\text{Ru}_2\text{Cl}_4(\text{benzene})_2]$ , p-cymene may substitute for benzene (page 5, column 8, line 8). Dependent Claim 16 is not obvious.

The Office Action stated: that, regarding Claim 17, US '665 teaches all of the elements of paragraph 12 above, regarding the formation of the ruthenium complex by mixing a compound of formula  $[\text{Ru}_2\text{Cl}_4(\text{cym})_2]$  with the Fluoxphos ligand (page 9, column 16, example 2); and that, as stated previously, the p-cymene ligand may substitute for the benzene (page 5, column 8, line 8). Dependent Claim 17 is not obvious.

The Office Action stated: that, regarding Claim 18, US '665 teaches all of the elements of paragraph 17 above, with regards to the preparation of the ruthenium-Fluoxphos complex by mixing of  $[\text{Ru}_2\text{Cl}_4(\text{cym})_2]$  with the Fluoxphos ligand (page 9, column 16, Example 2); and that the diethylamine counterion can be substituted with either  $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{I}^-$ ,  $\text{BF}_4^-$ ,  $\text{PF}_6^-$ , or  $\text{ClO}_4^-$ , (page 5, column 8, lines 8 to 11). Dependent Claim 18 is not obvious.

The Office Action stated: that, regarding Claim 19, US '665 teaches all of the elements of paragraph 5 above, and also that, when the hydrogenation is performed with the hydrogen pressure in the range of 1 to 150 bar (page 6, column 9, lines 17 to 19); and that this range falls within the hydrogen pressure range of 1 to 160 bar (preferably within 2 to 35 bar) that is specified by instant Claim 19. Dependent Claim 19 is not obvious.

The Office Action stated: that, regarding Claim 20, US '665 teaches all of the elements of paragraph 11 above, and additionally, that the hydrogenation is performed at a pressure range of 1 to 150 bar (page 6, column 9, lines 17 to 19); and that this falls

within the hydrogen pressure range of 1 to 60 bar (preferably within 2 to 35 bar) that is specified by instant Claim 20. Dependent Claim 20 is not obvious.

The Office Action stated: that, regarding Claim 21, US '665 teaches when the hydrogenation is carried out in a selection of C<sub>1-4</sub> alcohols, dimethylformamide, and additional solvent additives, with the ruthenium complex possessing at least one ligand of an alkene, diene, arene, or polar solvent molecule, the hydrogen pressure is in the range of 1 to 150 bar (page 6, column 9, lines 17 to 19); and that this falls within the hydrogen pressure range 1 to 60 bar (preferably within 2 to 35 bar) that is specified by instant Claim 21. Dependent Claim 21 is not obvious.

The Office Action stated: that, regarding Claim 22, US '665 teaches all of the elements of paragraph 17 (regarding instant Claim 14), with the additional stipulation that the hydrogenation is performed at a hydrogen pressure range of 1 to 150 bar (page 6, column 9, lines 17 to 19); and that this falls within the hydrogen pressure range of 1 to 60 bar (preferably within 2 to 35 bar) that is specified by instant Claim 22. Dependent Claim 22 is not obvious.

The Office Action stated: that, regarding Claim 23, US '665 teaches all of the elements of paragraph 21 above, with the additional stipulation that the hydrogenation is performed at a hydrogen pressure range of 1 to 150 bar (page 6, column 9, lines 17 to 19); and that this falls within the hydrogen pressure range of 1 to 60 bar (preferably within 2 to 35 bar) that is specified by instant Claim 23. Dependent Claim 23 is not obvious.

As shown above, none of the claims are obvious over the combination of rejection references.

This rejection should be withdrawn.

Reconsideration, reexamination and allowance of the claims are requested.

Respectfully submitted,

August 11, 2009  
Date

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<p align="center"><b>CERTIFICATE OF MAILING</b></p> <p>I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on <u>August 11, 2009</u>.</p> <p align="center"><u>Virgil H. Marsh</u> FISHER, CHRISTEN &amp; SABOL 1156 15th Street, N.W. Suite 603 Washington, D.C. 20005</p>
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